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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/812,292	03/29/2004	Dennis E. Discher	O-2863CIP	2280

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EXAMINER	
SILVERMAN, ERIC E	
ART UNIT	PAPER NUMBER
1618	

MAIL DATE	DELIVERY MODE
01/10/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/812,292	DISCHER ET AL.	
	Examiner	Art Unit	
	Eric E. Silverman, PhD	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *17-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11-15-07,10-29-07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' response to the election/restriction requirement, filed on 10/29/207 has been received.

Election/Restrictions

Applicant's election of Group I, claims 1 - 16 in the reply filed on 10/29/2007 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election **without traverse** (MPEP § 818.03(a)). Applicants general allegation that Groups II and III are "part and parcel" with Group I is not a distinct or specific allegation of error.

It is noted that the elected species is that of a mixture of PEO-lactide block copolymer and a PEO-butadiene block copolymer as the polymers for the vesicle, and doxorubicin as the theraputic encapsulant. Applicants have not stated which claims read on these species, but it is believed that claims 1 - 16 all read on the elected species.

Priority

It is noted that this application claims benefit of the filing date of Application 09/460,605, now US Patent 6,835,394. However, the aforementioned Application does not have support for instant claims; specifically, there is no mention of the instantly elected species. Accordingly, the references relied upon below in rejections over the prior art having publication dates after that of the '605 Application but before the

effective filing date of the instant Application are competent prior art under one or more sections of USC 102 against the instant application.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1 – 16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 states "high molecular weight". It is not clear what molecular weights are "high" as recited. The claim also states, in the last paragraph "the at least one inert, hydrophobic PEG-block copolymer". There is insufficient antecedent basis for this statement.

Claim 2 states PEG or "[a] structural equivalent thereof". It is not clear what materials, other than PEG, are structural equivalents thereof.

Claim 4 recites "high molecular weight". It is not clear what molecular weights are "high" as claimed. The claim is also confusing because it recites degradable polyesters "which when combined with PEG form[s] PEG-PLA [or PEG-PCL]". However, PLA and PCL do not form PEG-PLA or PEG-PCL, respectively, when combined with PEG. On the contrary, the copolymers are formed by using a functionalized PEG with one reactive endgroup, monomeric lactic acid or capralactone, and a catalyst, as in paragraph [0183] of the specification. They are also synthesized

by anioinic polymerization as in the Hillmyer reference (of record), as discussed in paragraph [0182] of the specification.

Claim 6 recites "increasing the mole fraction (mol%) of the at least one hydrolytically degradable block blended into the inert copolymer". It is not clear if this means that the amount of the block copolymer containing the hydrolytically degradable block is increased, or if it means that the percentage of hydrolytically degradable monomer in the block copolymer itself is increased (with a corresponding decrease in the percentage of PEO in the block copolymer). It is also not clear when or how the "increasing" step is to be performed. Based on the specification, it does not appear that the amount of any component of the vesicles can be increased after the vesicles are made. But during the manufacture of the vesicle, any hydrolytically degradable block added is not "increasing" the amount, but part of the "blending" step. It is not clear how this "increasing" step is different from the "blending" step recited in claim 1. Further, it is noted that mol% is not the same as mole fraction, though the claim makes the two appear to be the same. Mole fraction is the ratio of moles of the subcomponent of interest to the total moles, whereas mole% is the number of moles of the subcomponent of interest per one hundred total moles.

Claim 10 states "molecular weight from less than 10^2 Da to more than 10^5 Da". This is a range with neither upper nor lower limit, and thus is indefinite.

Claim 11 recites that the feo and polyester "primarily dictate release kinetics", but also that the molecular weight of the encapsulant also has an effect on release rate. It

is thus uncertain what is meant by "primarily dictate", as the claim indicates that the molecular weight of the encapsulant will have an effect on the release kinetics.

Claims 13 and 14 include recitations of "including" within a Markush group makes it unclear whether the claim is intended to be limited to the specific materials that are "included".

The remaining claims are rejected for directly or ultimately depending on one or more of the abovementioned claims without rectifying the issues, thereby incorporating the indefinite limitations of the parent claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1 – 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Piskin et al. J Biomater. Sci. Polymer Edn., 1995, of record in view of Won et al, Science, 1999, of record, and in further view of Discher et al, J. Phys. Chem. B, 2002, of record.

The elected species is method of making a mixed-micelle composition by adding to water a PEG-PLA block copolymer and a PEG-PBD (PBD being short for polybutadiene) block copolymer, wherein doxorubicin is encapsulated in the micelle. Claims 1 – 5, 7 – 9, 11 – 15 all read on this method with no additional steps required. Claim 6 is indefinite, as discussed above, and in its broadest reasonable interpretation the "increasing" step of this claim is the same as the "blending" step of claim 1, so this claim is just as broad in scope as claim 1. Claim 10 recites a range of molecular weights that includes any possible molecular weight, and so also encompasses everything included in claim 1. Claim 16 requires that the encapsulant be encapsulated either simultaneously with or subsequent to polymersome (vesicle) formation. Because the encapsulant clearly cannot be encapsulated by the polymesomes before the polymersomes are formed, this limitation is obviously and inherently be present in the elected method.

The Piskin reference teaches copolymer micelles as made from PEG-PLA (referred to in the article as PEG/PDLLA (abstract). These polymers are used to encapsulated doxorubicin (pages 367 and 370 under the heading *Drug loading and release*). According these sections of Piskin, the release of drug is controlled by the degradation of the PLA component of the micelles.

What is lacking is blending the PEG-PLA with PEG-PBD to form the micelles.

Won teaches that PEG-PBD (referred to as PEO-PB in the reference) is useful to make micelles (abstract). Won notes that PEG-PEE is also useful in micelle formation.

Discher teaches that it is known in the art to blend two different diblock copolymers, each separately useful in micelle formation, to form a single, mixed micelle (abstract). In particular, Discher suggests that PEG-PBD micelles are too stable to be useful in drug delivery, and suggests solving this problem by blending the PEG-PBD with another PEG-based diblock copolymer to make mixed micelles.

It would have been prima facie obvious to a person of ordinary skill in the art at the time of the invention to make a mixed micelle of PEG-PLA and PEG-PBD by blending the two in an aqueous media and to encapsulate doxorubicin within the resulting micelle. On one level, this combination represents little more than the combination of materials known for use for the same purpose in the art (namely to make micelles), which is generally obvious. On another level, the Discher reference advocates mixing different PEG based diblock copolymers in order to "tune" the properties of micelles, for example to decrease the stability of PEG-PBD micelles. The artisan, also being aware of the teachings of Piskin than PEG-PLA micelles degrade and release drugs, would recognize that such a degradable block copolymer would serve the purposes suggested by Discher, namely to decrease the stability of the PEG-PBD micelle, resulting in micelles with that are more suitable for drug delivery. Because the evidence of record indicates that the properties of the individual di-blocks as micelle formers are well understood, and the Discher reference supports the notion that the

artisan could readily mix two diblock copolymers, each of which forms micelles individually, and expect to obtain a micelle forming product, the artisan would enjoy a reasonable expectation of success.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eric E. Silverman, PhD whose telephone number is 571 272 5549. The examiner can normally be reached on Monday to Friday 7:30 am to 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward can be reached on 571 272 8373. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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